REMARKS

Reconsideration of the application is respectfully requested.

The listing of claims presented herein amends claims 27-34 and adds new claims 35-36. With entry of this amendment, claims 27-36 are pending in this application.

Support for the claim term "genetically modified" is found, for example, in original claim 2.

Support for the claim term "mouse" in claim 34 is found, for example, at page 4, lines 6-20.

Support for new claims 35 and 36 is found, for example, at page 4, lines 6-20; page 5, line 13 – page 8, line 17; and page 17, lines 24-26.

As stated in the Amendment and Response filed April 18, 2003, applicants have reserved the right to request rejoinder of claims directed to the subject matter of nonelected, cancelled claim 25 upon allowance of any of the pending claims.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

The Office rejected claims 27, 29, 31, and 33 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. The Office acknowledges that the specification is "enabling for a homozygous transgenic mouse whose genome comprises a knockout allele of the α-TTP gene wherein the mouse exhibits reduced fertility." (Office Action at page 2.) However, according to the Office, the specification "does not reasonably provide enablement for a heterozygous transgenic mouse whose genome comprises a knockout allele of the α-TTP gene wherein the mouse exhibits reduced fertility or for chimeric mice comprising cells comprising a knockout allele of the a-TTP gene." (Office Action at page 2.) Applicants respectfully traverse.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

The basis for the Office's rejection stems from the lack of any specified phenotype for the heterozygous and chimeric mice within claim 27. Specifically, the Office asserts that: (1) "[t]he specification fails to enable making and using a heterozygous mouse comprising a knockout allele of the α-TTP gene wherein the mouse has any phenotype" (Office Action at page 3); (2) "[t]he claim[s] fail to recite a phenotype for the heterozygous mouse and therefore [encompass] any and all phenotypes" (Office Action at page 3); and (3) "it would require one of skill in the art at the time the invention was made, undue experimentation to determine how to make and use a heterozygous mouse comprising a knockout allele of the α-TTP gene wherein the mouse displays any phenotype other than vitamin E deficiency" (Office Action at page 3).

However, the claims do not need to recite a phenotype to be enabling because the claims each recite a genotype that is fully enabled. Claim 27, and dependent claims 29, 31, and 33, recite transgenic mice comprising a knockout allele of the genomic α-TTP gene. The claims include the express limitation that the knockout allele is one in which expression of α-TTP from the knockout allele is inhibited such that transgenic mice homozygous for the knockout allele exhibit a vitamin E deficiency phenotype. Without limiting the scope of the claims in any way, applicants note the Examiner correctly characterizes the claims as encompassing, at least, chimeric mice comprising cells comprising a knockout allele of the genomic α-TTP gene, mice heterozygous for a knockout allele of the genomic α-TTP gene, and mice homozygous for a knockout allele of the genomic α-TTP gene. Thus, the genotype of the chimeric and heterozygous mice is clearly specified: the knockout allele of the genomic α-TTP gene that the claimed

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DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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chimeric and heterozygous mice comprise is modified such that expression of α-TTP from the knockout allele is inhibited and transgenic mice homozygous for the knockout allele exhibit a vitamin E deficiency phenotype. The Office acknowledges enablement of these homozygous mice. Thus, the subject matter of the claims is fully enabled because the claims do not encompass mice with "any phenotype" -- instead the claims encompass heterozygous and chimeric transgenic mice with the genotype that yields the recited phenotype for homozygous mice.

Moreover, there is no doubt that the specification fully enables the production of chimeric and heterozygous mice. Specifically, the application describes the generation of chimeric mice comprising cells comprising a knockout allele of the genomic α-TTP gene in Example 3, at pages 15-17. The application describes the generation of mice heterozygous for a knockout allele of the genomic α-TTP gene in Example 4, at pages 17-18. As described in Examples 5 and 6, at pages 18-21, when these chimeric and/or heterozygous mice are crossed to generate mice homozygous for a knockout allele of the genomic α-TTP gene, the homozygous mice exhibit a vitamin E deficiency phenotype. This means that the knockout allele of the genomic α-TTP gene that the claimed chimeric and heterozygous mice comprise is one in which expression of α-TTP from the knockout allele is inhibited such that transgenic mice homozygous for the knockout allele exhibit a vitamin E deficiency phenotype. Thus, Examples 3 and 4 teach how to make chimeric and heterozygous mice within the scope of claims 27, 29, 31, and 33. Accordingly, the specification fully enables claims 27, 29, 31, and 33.

Similarly, the application fully enables the use of such mice. Specifically, as described in Example 4, the chimeric mice comprising cells comprising a knockout allele

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HENDERSON
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GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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of the genomic α-TTP gene can be used to make mice heterozygous for a knockout allele of the genomic α-TTP gene. As further described in Example 4, the chimeric mice comprising cells comprising a knockout allele of the genomic α-TTP gene, and mice heterozygous for a knockout allele of the genomic α-TTP gene, can be crossed to make mice homozygous for a knockout allele of the genomic α-TTP gene. As described at page 1, lines 8-11, uses of these homozygous mice include development of methods or compositions to treat familial isolated vitamin E deficiency and oxidative stress-induced diseases such as arteriosclerosis and diabetes.

The Office recognizes that the disclosed use of the claimed homozygous mice satisfies the utility requirements of 35 U.S.C. §§ 101 and 112. As described above, the claimed chimeric and heterozygous mice are useful, at least, as intermediates for the production of these directly useful homozygous mice. Because the claimed chimeric and heterozygous mice are intermediates for the production of a useful final product, this use clearly satisfies the utility requirements of 35 U.S.C. §§ 101 and 112. *See Reiners v. Mehltretter*, 236 F.2d 418, 422 (C.C.P.A. 1956) ("Products are useful if they serve as starting materials or intermediates in producing other materials or articles which are directly useful.").

Accordingly, claims 27, 29, 31, and 33 are fully enabled by applicants specification, and Applicants respectfully request that the Examiner withdraw the rejection of the claims for lack of enablement.

The Office also alleged that "[t]he specification fails to enable making a heterozygous mouse comprising a knockout allele of the α-TTP gene wherein the mice exhibit a failure of pregnant females to maintain pregnancy as assayed by the fetal

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HENDERSON
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GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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resorption test (claim 29)." (Office Action at page 3.) Applicants respectfully traverse for all the reasons set forth above.

Moreover, to ensure clarity, claim 29 does not recite "a heterozygous mouse comprising a knockout allele of the α-TTP gene wherein the mice exhibit a failure of pregnant females to maintain pregnancy as assayed by the fetal resorption test." As set forth above, claim 29 does not limit the phenotype of heterozygous mice encompassed by it in any way. Claim 29 depends from claim 27, and the claim does not specify the phenotype of chimeric and heterozygous mice encompassed by the claim. Instead, the claim specifies the genotype of the chimeric and heterozygous mice encompassed by the claim by requiring that expression of α-TTP from the knockout allele is inhibited such that transgenic mice homozygous for the knockout allele exhibit a vitamin E deficiency phenotype, wherein the vitamin E deficiency phenotype comprises a failure of pregnant females to maintain pregnancy as assayed by the fetal resorption-gestation test.

With respect to claim 33, the Office concedes that the art at the time of filing enabled making chimeric mice generally, but then alleges that "one of skill in the art would not know how to use [the claimed] mouse." (Office Action at page 4.) As described above, these chimeric mice are useful independently of their phenotype -- they can be used at least to make heterozygous and homozygous mice comprising a knockout allele of the genomic α-TTP gene. Because such homozygous mice are useful to develop methods and compositions of treatment, the chimeric mice are useful as intermediates. *See Reiners v. Mehltretter*, 236 F.2d 418, 422 (C.C.P.A. 1956) ("Products are useful if they serve as starting materials or intermediates in producing other materials or articles which are directly useful."). Thus, applicants have taught how

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

to use the claimed mouse and satisfied the enablement requirement of 35 U.S.C. § 112, first paragraph.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

The Office rejected claims 27-34 under 35 U.S.C. § 112, second paragraph, because the Office alleges that the claims are indefinite, for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. (Office Action at pages 4-5.) Applicants respectfully traverse.

First, the Office concludes that "[c]laim 27 is unclear because it encompasses both heterozygous and homozygous mice wherein only the homozygous mice have a phenotype." (Office Action at page 5.) However, this conclusion is not an issue of indefiniteness. Indeed, the Office has correctly recognized that the claim encompasses both heterozygous and homozygous mice. As described above, heterozygous mice encompassed by claim 27 are fully enabled and the Office has understood its scope. Applicants submit that claim 27 is not indefinite.

The Office concluded that claims 27-32 are indefinite "because it is not known whether the claim[s] intend[ ] to encompass chimeric mice made by the method of dependent claim 33." (Office Action at page 5.) The Office went on to allege that "[i]t is well known in the art that a transgenic animal is one whose somatic and germ cells comprise a transgene and is not chimeric." (Office Action at page 5.) First, applicants respectfully point out that claim 33 depends from claim 27, reciting "A method for producing the mouse according to claim 27 . . . ." Thus, claim 27 must necessarily encompass mice made by the method of claim 33. Nonetheless, in the interest of

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

expediting the prosecution of this application and the allowance of the pending claims, applicants have amended the claims herein to recite "genetically modified" instead of "transgenic". Applicants submit that this amendment does not change the scope of the claims but does obviate any basis the Office has for finding the claim indefinite.

Applicants thank the Office for the suggested claim language and have adopted it in new claims 35 and 36, which recite "A genetically modified mouse whose somatic and germline cells comprise a knockout allele of the genomic α-TTP gene . . ." and "A genetically modified mouse whose somatic and germline cells are homozygous for a knockout allele of the genomic α-TTP gene . . . ," respectively.

According to the Office, claims 29, 31, and 33 are unclear because they refer to "'The transgenic mouse according to claim 27', however, claim 27 encompasses two different mice, a heterozygous and a homozygous mouse." (Office Action at page 5.) As set forth above, claim 27 does encompass heterozygous and homozygous mice; however, this claim scope is fully enabled and, as the Office has correctly recognized, clearly encompasses, at least, both heterozygous and homozygous mice. Applicants submit that claims 29, 31, and 33 are clear, proper dependent claims that each further limits claim 27. Applicants respectfully request that the Examiner withdraw this rejection.

The Office also rejected claim 33 "because it is a method of making a chimeric mouse; however, claim 33 depends from claim 27, which is drawn to a transgenic mouse that, by definition, is not chimeric." (Office Action at page 5.) As described above, applicants have amended claim 27 to recite "genetically modified." As such,

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

claim 27 encompasses chimeric mice and thus claim 33 is clear as it depends from claim 27. And, for all the reasons set forth above, it is fully enabled.

Finally, the Office rejected claim 34 because the claim referred variably to "mice" and "non-human mammal." Applicants have amended claim 34 to refer to mice throughout, thus obviating the basis for this rejection.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims 27-36. If this paper does not put the claims in condition of allowance, the Applicants urge the Examiner to contact the undersigned at 650-849-6607.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: Deborah Kate #51,823
for Jean B. Fordis
Reg. No. 32,984

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com